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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/503,596	02/11/2000	Mu-en Lee	05433-042001	6895

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EXAMINER	
CHONG, KIMBERLY	
ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 10/18/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/503,596	LEE ET AL.	
	Examiner	Art Unit	
	Kimberly Chong	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) _____ is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,5,6 and 9-12* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicant's election without traverse of claims 1-3, 5, 6 and 9-12 is acknowledged.

Claims 25 and 26 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made without traverse.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 1 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is indefinite for failing to distinctly claim the coding sequences of SEQ ID NO 2. Claim 1 recites the limitation "a coding sequence of SEQ ID NO:2." This implies there are multiple coding regions of SEQ ID NO:2 which from the specification as filed the sequence is a human cDNA and by character can only have a single coding region.

Claims 1-3, 5, 6 and 9-12 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Applicant's arguments filed 11/06/03 have been fully considered but they are not persuasive.

The claims are drawn to methods of inhibiting formation of an atherosclerotic lesion in a mammal or inhibiting differentiation of a macrophage into a foam cells via administration to a mammal a compound (SEQ ID NO: 2) that reduces expression of AFABP, specifically SEQ ID NO 4. The specification as filed teaches a mouse model with a knock-out of AFABP and the correlation between a decrease in the expression of AFABP in macrophage-derived foam cells and a decrease in atherosclerotic lesions.

The arguments raised in the Official Action dated 5/6/03 were drawn to the lack of guidance in the specification for successful delivery of the antisense compound to the atherosclerotic lesion and the unpredictability known in the antisense art for therapeutic, *in vivo* applications. Specifically the specification does not teach (1) stability of the antisense molecule *in vivo*, (2) delivery to the whole organism and specificity to the target tissues, (3) dosage and toxicity, nor (4) entry of molecule into cell and effective action therein marked by visualization of the desired treatment effects. There is no guidance in the specification as filed that teaches how the claimed antisense compounds enter the human macrophage cell, inhibit the expression of AFABP, prevent

the human macrophage from differentiating into a foam cell and ultimately inhibit atherosclerotic lesions.

Applicants state on page 8 of the response filed 11/06/03 that they "provide an assay, namely the differentiation of macrophages into foam cells, which can be used to measure effective concentration and specificity of antisense oligonucleotides."

It is not sufficient that merely providing an assay, "namely the differentiation of macrophages into foam cells", will provide one skilled in the art with a sufficient level of guidance to make and use the claimed invention. As taught by the references cited in the Official Action mailed 8/14/02, it is not predictable that an antisense which inhibits a target gene in cells in culture will function equivalently in a whole organism in view of the numerous unpredictable considerations found in a whole organisms (as argued above). Furthermore, Crooke supports the difficulties of interpreting *in vitro* cellular assays and points out that "clear demonstration of the antisense mechanisms are required before drawing conclusions from *in vitro* experiments (page 471, col. 1)."

Applicants further state on Page 8 of the response filed 11/06/03 that providing the assay stated above "and the art-recognized mouse model disclosed in the specification, coupled with the knowledge of those skilled in the art of gene expression technology, enables the determination of effective concentration, specificity, and toxicity of antisense oligonucleotides suitable for the inhibition of macrophages into foam cells and the resultant formation of atherosclerotic lesions....Therefore, Applicants submit that they have provided adequate guidance for determining the factors presented in the

cited references, *i.e.* concentration, toxicity, specificity of binding, and rate of degradation."

Although Applicant has provided evidence, via the knock-out mouse model, that there is a correlation between decreased levels of AFABP and decreased atherosclerotic lesions, the knock-out model does not teach how to deliver the claimed antisense compound to the macrophage cells *in vivo* and how this antisense compound will inhibit the expression of the AFABP which will then lead to a decrease in atherosclerotic lesions. The teachings of the knock-out mouse do not provide adequate guidance for determining concentration, toxicity, specificity of binding and the rate of degradation, such that any kind of AFABP inhibition in vivo could be predicted, and further that inhibition of atherosclerotic lesion formation would be provided. As stated in the previous Office Action mailed 8/14/02, there is a high level of unpredictability in the art for making and using antisense in whole organisms and further where treatment effects might be obtained. Because there is no specific guidance taught by the knock-out mouse model, the specification as filed or the prior art, one skilled in the art would have to engage in and practice trial and error experimentation to discover antisense that are able to target AFABP, in a whole animal, in such a manner as to provide the claimed functions, namely inhibition of atherosclerotic lesions.

Applicants state on Page 7 of the response filed 11/06/03 that "[o]ne reasonably skilled in the art could make and use the invention from the disclosures in the application coupled with information known in the art without undue experimentation. With respect to making the antisense oligonucleotides, Applicants have provided the

target sequences and an antisense sequence." Applicants further state that "[m]ethods to increase antisense oligonucleotides stability are also discussed" and "[w]ith respect to using the antisense oligonucleotides, a macrophage-specific promoter, scavenger receptor A gene promoter, is disclosed, as well as appropriate vectors for use in antisense treatment." Applicants also state that "[d]elivery systems, such as liposomes, receptor-mediated delivery systems, non-viral nucleic acid-based vectors, erythrocyte ghosts, and microparticles, are disclosed in the specification at page 10, lines 6-12, and are well-known and used in the art....Therefore, one skilled in the art of antisense could make and use the invention as claimed."

While one skilled in the art may be able to find an antisense sequence to AFABP, the specification as filed does not teach how to administer any antisense to inhibit atherosclerotic lesions as claimed. Applicants further state on Page 8 of the response filed 11/06/03 that "this is the type of experimentation that those skilled in the art routinely perform." To practice the claimed invention, one of skill in the art would have to *de novo* determine; the stability of the antisense molecule *in vivo*, delivery of the antisense molecule to the whole organism, specificity to the target tissue *in vivo*, dosage and toxicity *in vivo*, and entry of the molecule into the cell *in vivo* and the effective action therein. Without further guidance, one of skill in the art would have to practice a substantial amount of trial and error experimentation, an amount considered undue and not routine, to practice the instantly claimed invention.

Therefore, in considering the sum total of the evidence, they do not teach how the claimed antisense compounds enter the human macrophage cell, inhibit the

expression of AFABP, prevent the human macrophage from differentiating into a foam cell and ultimately inhibit atherosclerotic lesions. Thus, the specifications as filed do not provide guidance on how to overcome the high level of unpredictability in the art for design of any such antisense therapeutic compound.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kimberly Chong whose telephone number is 571-272-3111. The examiner can normally be reached Monday thru Friday between 7-4 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader can be reached at 571-272-0760. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It

also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public. For more information about the PAIR system, see http://pair-direct.uspto.gov.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Kimberly Chong
Examiner
Art Unit 1635

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